

**Supplemental Response letter for application 10/037, 718 following recently filed RCE, 2  
Amend/Resp of 2/5/2007 submitted by fax 571-273-8300 Feb. 12, 2007 This letter is 2  
pages long.**

Specifically these documents are 5 pages: (1) the marked definition of Linkage from the online Genome Glossary of the U.S. Government's Human Genome Project dated 1/30/2007, and two marked pages from the Encyclopedia of Molecular Biology and Molecular Medicine (1996) editor Robert A. Meyers. Page 377 (2), volume 3 of the Encyclopedia defines Linkage (of genes), and on page 222 (3) volume 1 of the Encyclopedia under Linkage Analysis the Encyclopedia describes linkage of a marker and gene. Also included are (4) the Title page of the first volume of the Encyclopedia of Molecular Biology and Molecular Medicine and (5) a bibliographic page of the Encyclopedia that indicates year of publication, publisher, editor, and ISBN. The above described 5 pages are included with this fax submission.

Respectfully submitted,



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## Human Genome Project Information

### Genome Glossary

#### All Terms

A B C D E F G H I J K L M N O P Q R S T U V W X Y Z

## L

#### Library

An unordered collection of clones (i.e., cloned DNA from a particular organism) whose relationship to each other can be established by physical mapping.

See also: [genomic library](#), [arrayed library](#)

#### Linkage

The proximity of two or more markers (e.g., genes, RFLP markers) on a chromosome; the closer the markers, the lower the probability that they will be separated during DNA repair or replication processes (binary fission in prokaryotes, mitosis or meiosis in eukaryotes), and hence the greater the probability that they will be inherited together.

#### Linkage disequilibrium

Where alleles occur together more often than can be accounted for by chance. Indicates that the two alleles are physically close on the DNA strand.

See also: [Mendelian inheritance](#)

#### Linkage map

A map of the relative positions of genetic loci on a chromosome, determined on the basis of how often the loci are inherited together. Distance is measured in centimorgans (cM).

#### Localize

Determination of the original position (locus) of a gene or other marker on a chromosome.

#### Locus (pl. loci)

The position on a chromosome of a gene or other chromosome marker; also, the DNA at that position. The use of locus is sometimes restricted to mean expressed DNA regions.

See also: [gene expression](#)

K

Encyclopedia of Molecular  
Biology and Molecular Medicine  
Volume 3 (1996) Editor  
R. A. Meyers

## KALLIKREIN-KININOGEN-KININ SYSTEM

Michael E. Rusiniak and Nathan Back

- 1 The Kallikrein-Kininogen-Kinin (K-K-K) System
  - 1.1 The K-K-K Protease Cascade
  - 1.2 Physiological Functions of the K-K-K System
  - 1.3 The K-K-K System in Pathology
- 2 Structure, Function, and Molecular Biology of K-K-K System Components
  - 2.1 Kininogens
  - 2.2 Kallikreins
  - 2.3 Kinin Receptors

### Key Words

**Crossing Over** The reciprocal exchange of material between homologous regions of chromosomes during meiosis; a DNA strand of one parental molecule exchanges base-pairs with a complementary region of a DNA strand from another molecule with which it is being paired.

**Domain** A contiguous stretch of amino acids within a protein sequence related to a functional property of the molecule.

**Gene Conversion** Modification by DNA repair of a mismatched strand of heteroduplex DNA during meiosis; this process results in generation of an extra copy of one of the recombining genes.

**Hageman Factor** The plasma enzyme precursor that undergoes reciprocal activation with prekallikrein at the start of the intrinsic pathway of blood clotting.

**Linkage** The tendency of genes to be inherited together based on proximity within the same chromosome.

**Recombination** Either general (requiring homologous DNA) or site-specific (protein-mediated, not requiring sequence homology) exchange of DNA regions between chromosomes.

**Unequal Crossing Over** A recombination event in which the location of recombining sites is not identical in the parental DNAs.

Mammalian blood contains three major protease cascade systems interrelated through a shared Hageman factor activation mechanism: namely, the blood coagulation, fibrinolysin, and kallikrein-kininogen-kinin (K-K-K) systems. Components of the K-K-K protease cascade system present in blood and a number of different tissues include kinin-forming enzymes, the kallikreins, the glyco-

protein kinin-containing kininogen substrates, biologically active polypeptide kinins and kinin-destroying enzymes, the kininases. The K-K-K system functions, in part, via formed kinins that regulate tissue local blood flow, functional hyperemia and transmembrane ion transport. Plasma kallikrein and kininogen, in collaboration with Hageman factor, help initiate the intrinsic pathway of blood coagulation by contact activation mechanisms. In addition, novel functions of kininogens have been discovered recently; namely, cysteine proteinase inhibition and (in the rat) involvement in the acute phase response. By virtue of the diverse actions of kinins and other system components, the K-K-K protease cascade also is implicated in a wide variety of pathologic conditions.

Recent molecular technologies have enabled the characterization of the molecular biology of K-K-K system components, notably the kallikreins and kininogens, and to a lesser extent, kinin receptors. Whereas plasma kallikrein is encoded by a single gene in the liver, a larger family of glandular kallikrein genes, particularly in rodent species, has undergone concerted evolution to yield a family of enzymes with divergent substrate specificities. Expression of kallikrein genes is tissue specific and developmentally regulated. Kininogens are multidomain, multifunctional proteins. High molecular weight kininogen (HMWK) and low molecular weight kininogen (LMWK) are derived from alternative splicing of a single gene. The region of the modern kininogen gene encoding the heavy chain is proposed to have evolved from the stefin gene progenitor of the mammalian superfamily of cysteine proteinase inhibitors. The present-day kininogen gene also has acquired regions encoding the kinin moiety and a light chain that endows HMWK with a cofactor role in the intrinsic blood coagulation cascade. A third type of kininogen, T-kininogen (found only in the rat), is considered to be derived from an ancestral gene in common with HMWK and LMWK. T-Kininogen is expressed at elevated levels during acute inflammation, whereas the production of HMWK and LMWK remains unchanged. The mechanisms governing the development and regulated expression of K-K-K system components are being elucidated and will enhance our understanding of the role of this protease cascade in health and disease.

## 1 THE KALLIKREIN-KININOGEN-KININ (K-K-K) SYSTEM

### 1.1 THE K-K-K PROTEASE CASCADE

Plasma and tissue pathways of kinin formation, the ultimate end product of K-K-K system activation (Figure 1), are embodied in a cascading sequence of limited proteolysis in which the product of one proteolytic action acts as catalyst for the subsequent reaction (Figure 2). The specific kinin-forming plasma or tissue protease kallikrein selectively cleaves kininogen substrate to liberate vasoactive peptide kinins that bear the canonical bradykinin nonapeptide sequence. These vasoactive kinins have localized and short-

## 222 Breast Cancer, Genetic Analysis of

Danish data, which had been collected by Jacobsen in the midst of World War II, led Andrieu et al. to reject the model of dominant Mendelian inheritance for this sample of families (containing cases of breast cancer only or with another type of cancer). In their report published in 1988, these investigators did not, however, reject this hypothesis for the subsample of families affected only by breast cancer.

Using American data, Goldstein et al. suggested in 1988 that heterogeneity might be related to the interval between diagnoses of the two primary tumors in probands with bilateral breast cancer. Families in which the proband's two primary tumors were diagnosed within one year (synchronous) showed segregation of breast cancer consistent with recessive inheritance. For families of probands with asynchronous breast cancer, transmission was consistent with autosomal dominant inheritance.

In 1990 the same team performed a new study that classified the cancers histologically (ductal cancer, lobular cancer, adenocarcinoma, and medullary cancer) and distinguished between the pre- and postmenopausal cases. In the ductal subsample, a recessive gene was sufficient to explain the breast cancer distribution when the proband's case was postmenopausal. In contrast, when the proband had premenopausal (ductal) breast cancer, the transmission model was consistent with a dominant major gene, with sporadic cases of disease.

Also in the late 1980s, Bishop et al. analyzed nine Utah pedigrees chosen for a cluster of breast cancer cases. No clear fit of any genetic model was possible.

Segregation analyses of breast cancer, then, have led to divergent conclusions. These differences probably arise from the method by which the families were selected for study and the diversity of their origin; in addition, the type of information considered (sex, age at onset, bilateral cancers, presence of another type of cancer, etc.) varied from one study to another.

In more recent American and British segregation analyses of a large number of affected women and their female first-degree or first- and second degree relatives, three research teams, Newman, Claus, and Iselius and their colleagues independently reached identical conclusions, namely, that a mixture of two distributions best explains the data:

1. One distribution corresponds to the presence of a low frequency, predisposing allele (considered to be a mutation), transmitted in an autosomal dominant fashion, with a nearly complete penetrance at age 80 for its carriers ("genetic cases"). In other words, the women carrying this mutation have an almost 100% probability of developing breast cancer if they live beyond the age of 80 years.
2. The other distribution corresponds to cases that are not genetically determined, which appear in a completely random manner ("sporadic cases"). The probability that a woman without the disease allele will develop the disease is about 10% for a life span of 80 years.

According to these analyses, approximately 5% of cases are "genetic" and 95%, "sporadic." From this, we can deduce that when the mutation segregates in a family, each daughter of a woman carrying it has a 50% probability of inheriting it: a high concentration of cases would be observed in such a family. Inversely, the risk of developing breast cancer for relatives of a woman who is affected by the disease but does not carry the mutation is the same as that of any individual in the general population. Only a small number of cases

would be observed in these families. The families containing only one or a few cases represent the vast majority of those affected by the disease.

Even when the mutation is present in a family, all the affected women are not necessarily genetic cases: certain cases may be sporadic. Similarly, breast cancer can very easily appear in a sporadic fashion in two close relatives. The existence of so great a number of sporadic cases may lead to a lack of power to demonstrate a genetic subentity.

Although the segregation analyses performed by Newman et al. and by Claus et al. lead to the same general conclusions, they nonetheless present variations affecting the estimation of parameters (the mutation's frequency and penetrance values).

Table 1 presents the estimations obtained in these two studies. In both sets of results, the probability of developing the disease is strongest:

at a young age for carriers of the mutation  
at an older age for noncarriers

## 2 LINKAGE ANALYSIS

### 2.1 USE OF A GENETIC MARKER

Sequences of DNA whose location on the genome is known are referred to genetic markers. A great many markers, located all over the genome, are presently known and used for linkage analysis. At the same location, the sequences of a marker can vary according to the individual; different forms are called marker alleles. A marker is most interesting and most useful when it exists in a large number of alleles (i.e., when it is polymorphic). When a gene, an allele of which carries a mutation responsible for the appearance of a pathology, is located on the same chromosome pair as a marker and close to it (i.e., when gene and marker are genetically linked), the alleles on the same chromosome are generally transmitted together within a family: that is, they cosegregate. The transmission, or segregation, of the marker's alleles (i.e., the fashion in which the alleles are transmitted from one generation to the next) allows investigators to follow the segregation of the mutation indirectly.

Table 1 Values of Parameters  $S1^a$  and  $S2^b$  for Each Age Group ( $q, P, P'$ )

Age Class $i$	$S1,$ $q = 0.01$		$S2,$ $q = 0.003$	
	$P_i$	$P'_i$	$P_i$	$P'_i$
20-30			0.0167	0.0002
30-40	0.37	0.004	0.1277	0.0025
40-50			0.2314	0.0111
50-55	0.29	0.024		
55-60			0.1719	0.0137
60-70			0.1266	0.0222
70-80	0.16	0.053	0.2709	0.0301
80+			0.0548	0.0456

<sup>a</sup>Data from Newman, B., Austin, M. A., Lee, M., and King, M. C. (1988). Inheritance of human breast cancer: Evidence for autosomal dominant transmission in high risk families. *Proc. Natl. Acad. Sci. USA*, 85:3044-3048.

<sup>b</sup>Data from Claus, E.B., Risch, N., and Thompson, W. D. (1991). Genetic analysis of breast cancer in the cancer and steroid hormone study. *Am. J. Hum. Gen.* 48:232-242.

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# Encyclopedia of Molecular Biology and Molecular Medicine

## Volume 1

Achilles' Cleavage to Cytoskeleton-Plasma Membrane Interactions

*Edited by*

Robert A. Meyers



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